ANAPHYLACTIC SHOCK IN DOGS *

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The rapid and pronounced fall in blood pressure which is characteristic of anaphylactic shock in the dog was first observed by Richet[1] in his studies on congestion.

This phenomenon, which constitutes the only constant feature when the animal is anesthetized, was carefully studied by Biedl and Kraus.[2] They sensitized dogs by the injection subcutaneously of from 3 to 5 c.c. of horse or ox serum, and 21 days later gave 10 c.c. of the same serum intravenously. After an interval of from 10 to 15 seconds the blood pressure fell from the normal, 150 to 180 mm. of mercury, to 80 or even 40 mm. During this stage stimulation of the peripheral end of the splanchnic nerve and the intravenous injections of from 0.1 to 0.2 mg. of epinephrin caused either no rise, or only a slight rise, in blood pressure. Barium chlorid, on the other hand, by its power of vasoconstriction, raised the pressure and stopped the symptoms. From this they concluded that the fall in pressure was due to vasodilatation caused by injury to the peripheral vasomotor apparatus. They did not believe that the heart was in any way concerned in the process. In their further studies they still adhered to this view.[3]

This conclusion of Biedl and Kraus has been accepted by most other investigators, notably by Pearce and Eisenbrey,[4] Edmunds,[5] and others. Pearce and Eisenbrey further localized the injury in the nerve endings rather than in the muscular coat of the vessel wall. They think, however, that these structures are not completely paralyzed, but that their activity is greatly diminished as shown by the slight reaction to epinephrin and stimulation of the splanchnic nerve. The fall in blood pressure is due to the accumulation of the blood in the large venous trunks and the vessels of the splanchnic area as a result of vasodilatation, so that not enough blood reaches the heart to keep up the pressure in the systemic circulation.

Robinson and Auer,[6] by use of the electrocardiogram, found evidence that anaphylactic shock in the dog may produce definite cardiac disturbances in addition to the peripheral vasomotor paralysis.

W. H. Schultz,[7] working chiefly with cats and to a less extent with dogs, offers a quite different explanation for the fall in blood pressure in anaphylactic shock. According to his view, the injection of the second dose of serum causes

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[1] Compt. rend. Soc. de biol., 1905, 58, p. 112.
[2] Wien. klin. Wchnschr., 1909, 22, p. 363.
[3] Ztschr. f. Immunitätsf., 1910, 7, p. 205.
[4] Jour. Infect. Dis., 1910, 7, p. 565.
[5] Ztschr. f. Immunitätsf., 1913, 17, p. 105; 1914, 22, p. 181.
[6] Jour. Exper. Med., 1913, 18, p. 556.
[7] Jour. Pharm. and Exper. Therap., 1912-13, 3, p. 299. Bull. Hyg. Lab., P. H. and M.-H. S., No. 80, 1912.

a marked constriction of the vessels of the lungs. This is so extreme that too little blood reaches the left side of the heart to maintain the pressure in the systemic vessels. The accumulation of blood in the large venous trunks and in the splanchnic area is, according to Schultz, "for the most part purely passive." This view has apparently been accepted by Dale[8] and Airila;[9] but it has been severely criticized and apparently refuted by Pearce and Eisenbrey,[10] and by Edmunds.[5]

While the best evidence indicates that the fall in blood pressure in anaphylactic shock in the dog is due to injury of the nerve endings in the vessel walls, it seemed desirable to determine also the condition of the sympathetic nervous system, a possible factor which has hitherto been more or less completely neglected. In the course of experiments conducted for this purpose results were obtained which were thought to be of sufficient interest to warrant their report.

A healthy dog was given a subcutaneous injection of 2 c.c. of normal horse serum. Three weeks later the animal was anesthetized with ether, and the carotid or femoral artery connected with a mercury manometer. The normal reactions of the animal to intravenous injections of standard doses of epinephrin (0.5 c.c. of a 1:20,000, or 1 c.c. of a 1:50,000 solution) and of nicotin (0.5 c.c. of a 1:2000, or 1 c.c. of a 1:4000 solution), were first obtained. These reactions were shown by Hoskins and Wheelon[11] to be "sufficiently constant for a given animal to permit their use as criteria of activity and irritability of the sympathetic nervous system."

After the normal reactions had been recorded, the animal was given from 4 to 6 c.c. of normal horse serum intravenously, the serum being washed into the vein with from 6 to 8 c.c. of normal salt solution. There was an immediate slight rise in pressure, due to the volume of fluid injected, with a prompt return to normal. Within from 10 to 30 seconds in nearly all the animals the blood pressure began to fall and, in about the same period of time, it had reached its lowest level. At intervals of from 1 to 3 minutes thereafter intravenous injections of standard doses of epinephrin and nicotin were given. In a few animals barium chlorid and pituitrin were also used, the former producing in none of my animals the prompt recovery mentioned by Biedl and Kraus.

The amount of fall in pressure varied, but usually amounted to from 50 to 80 mm. of mercury. In fatal cases pressures as low as 20 to 30 mm. of mercury were obtained. In such animals respiration stopped while the heart was still active. None of these fatal cases is included in the series here reported. The duration of the period of low blood pressure varied from a few minutes to more than 3 hours in one instance (Dog A 10. Chart 2).

Altogether 11 animals were thus observed. The results in 2 animals are shown in Charts 1 and 2. From these and other tracings not presented the following facts are evident:

[8] Jour. Pharm. and Exper. Therap., 1912, 3, p. 167.

[9] Skandin. Arch. f. Physiol., 1914, 31, p. 388. Abstracted in Zentralbl. f. Physiol., 1914, 29, p. 15.

[10] Jour. Pharm. and Exper. Therap., 1912-13, 4, p. 21.

[11] Am. Jour. Physiol., 1914, 34, p. 81.

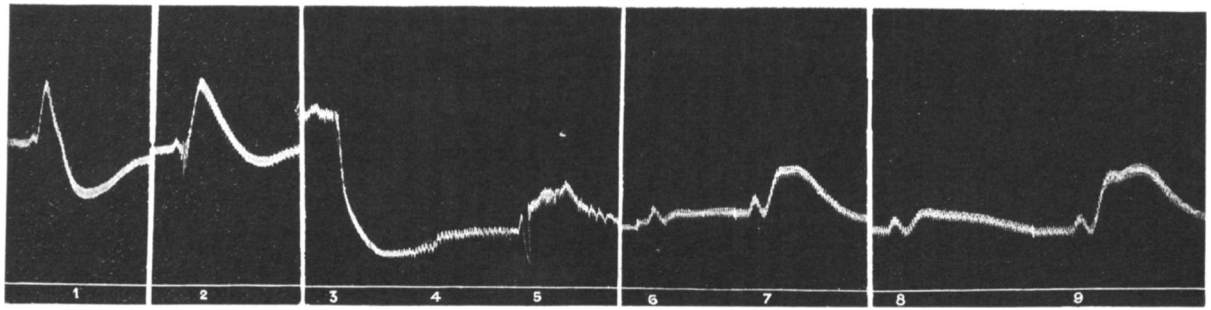

CHART 1

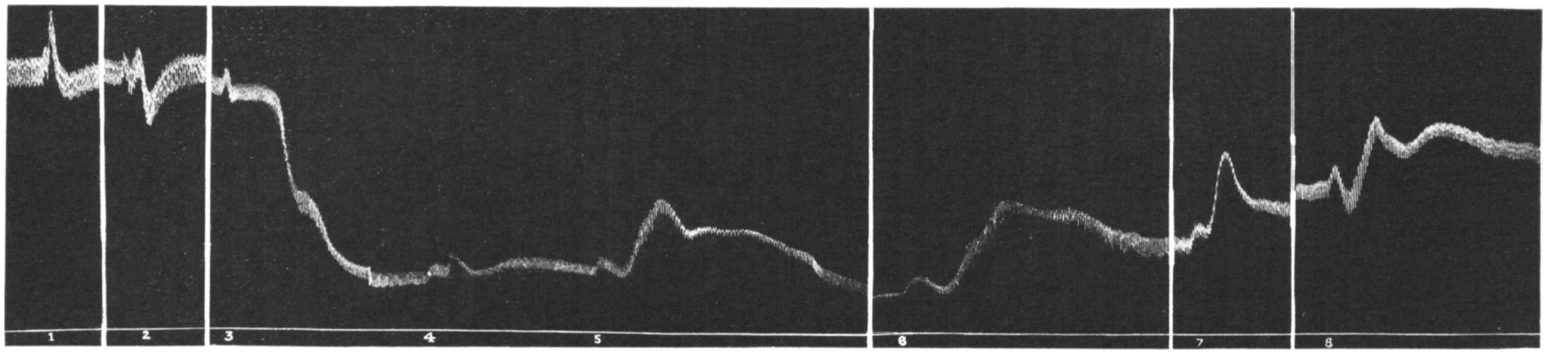

CHART 2

CHART 1

Dog A8. Given subcutaneous injection of 2 c.c. of normal horse serum, Nov. 25, 1914. Anaphylactic shock induced by intravenous injection of 6 c.c. of normal horse serum, Dec. 16, 1914.

1. Normal reaction to 0.5 c.c. of a 1:20,000 adrenalin solution.
2. Normal reaction to 0.5 c.c. of a 1:2000 nicotin solution.
3. Intravenous injection of 6 c.c. of normal horse serum at 3:05 p. m.
4. 0.5 c.c. of adrenalin solution at 3:07 p. m.
5. 0.5 c.c. of nicotin solution at 3:08 p. m. Marked dyspnea.
6. 0.5 c.c. of adrenalin solution at 3:45 p. m.
7. 0.5 c.c. of nicotin solution at 3:47 p. m. Moderate dyspnea.
8. 0.5 c.c. of adrenalin solution at 4:19 p. m.
9. 0.5 c.c. of nicotin solution at 4:24 p. m. Moderate dyspnea.

CHART 2

Dog A10. Given subcutaneous injection of 2 c.c. of normal horse serum, Dec. 19, 1914. Anaphylactic shock induced by intravenous injection of 7 c.c. of normal horse serum, Jan. 9, 1915.

1. Normal reaction to 0.5 c.c. of a 1:20,000 adrenalin solution.
2. Normal reaction to 0.8 c.c. of a 1:2000 nicotin solution.
3. Intravenous injection of 7 c.c. of normal horse serum at 11:16 a. m.
4. 0.5 c.c. of adrenalin solution at 11:19 a. m.
5. 0.8 c.c. of nicotin solution at 11:21. Dyspnea.
6. 0.8 c.c. of nicotin solution at 11:29 a. m. Animal was practically moribund when the injection was made. Marked dyspnea followed. Blood pressure rose from 26 to 88 mm. of mercury.
7. 0.5 c.c. of adrenalin solution at 11:36 a. m., 20 minutes after onset of shock.
8. 0.8 c.c. of nicotin solution at 11:41 a. m. Pressure reached normal level 36 minutes after onset of shock.

1. Immediately after the blood pressure has reached its lowest level, there is no response to injections of either epinephrin or nicotin.

2. As time elapses, the reaction to nicotin reappears before the response to epinephrin. This may occur before the blood pressure begins to show any upward trend.

3. The ability to react to injections of nicotin returns more rapidly than the ability to react to epinephrin, and, in most instances, becomes markedly exaggerated. This usually takes place at a time when the response to epinephrin is still weak or even absent.

In producing vasoconstriction and consequent rise in blood pressure, pituitrin is believed to act directly on the muscular coat of the vessel walls while epinephrin stimulates the nerve endings.[12] The pressor effect of nicotin was shown by Hoskins and Ranson[13] to be "due about half to a stimulation of the vaso-constrictor (vaso-reflex?) center proper, and half to stimulation of the ganglion cells."

If the fall in blood pressure in anaphylactic shock in the dog is due to a paralysis of, or injury to, the nerve endings in the vessel walls, as suggested by Biedl and Kraus and by Pearce and Eisenbrey, it is difficult to account for the fact that there is an earlier return of reaction to nicotin than to epinephrin. The continued low pressure is due to the accumulation of blood in the large veins and vessels of the splanchnic area so that too little blood reaches the heart to enable it to keep up the arterial pressure. The action of nicotin must in some way reduce the amount of blood in these areas and increase the volume which reaches the heart. There are two possible ways in which this might be accomplished: (1) by causing a vasoconstriction of the vessels concerned; and (2) by action on respiration.

It has been shown that at a time when the reaction to epinephrin is very weak the response to nicotin may be greatly exaggerated. Hoskins, Rowley, and Rosser[14] found that in conditions of low pressure due to hemorrhage, the reaction to nicotin was augmented. In their animals the response to epinephrin remained normal. Since they observed the same phenomena in otherwise normal animals with both carotids ligated, they concluded that these results were due to increased irritability of the vasomotor center brought about by anemia of that center. In the condition of anaphylactic shock, however, the pressor effect of epinephrin is either absent or greatly diminished at a time

[12] Pearce and Eisenbrey: Arch. Int. Med., 1910, 6, p. 218. Brodie and Dixon: Jour. Physiol., 1904, 30, p. 476.

[13] Jour. Pharm. and Exper. Therap., 1915, 7, p. 375.

[14] Arch. Int. Med., 1915, 16, p. 456.

when nicotin may cause an exaggerated rise in pressure. In other words, a pressor drug which acts on the nerve endings in the vessel walls produces no effect or one greatly reduced, while the pressor effect of a drug which acts on the vasomotor center and on the ganglion cells is increased. This is especially well demonstrated in Chart 2. This animal (A10) was apparently moribund when the injection of a standard dose of nicotin caused a rise of 60 mm. of mercury, and the animal ultimately recovered from the shock.

In explanation of this anomalous reaction, it is possible that the vasomotor center (including the sympathetic ganglia) is in a state of increased irritability. This condition may be caused by anemia of the center due to the low blood pressure. It was not due to occlusion of one of the carotids by connection with the manometer, for similar results were obtained when the manometer was connected with the femoral artery and the carotids left untouched. Whether the toxin (anaphylatoxin) which causes the shock may also increase the irritability of the vasomotor center, from the facts at hand can neither be affirmed nor denied. It does not appear necessary to presuppose such an action in order to explain the facts.

In this connection it is interesting to note that Beifeld, Wheelon, and Lovelette[15] recently reported studies on the influence of hypotensive gland extracts on vasomotor irritability. After injections of extracts of pancreas and salivary glands they obtained a fall in blood pressure with the same characteristics as the low pressure in anaphylactic shock, namely, a decreased reaction to epinephrin and an augmented reaction to nicotin. They conclude that "such extracts cause therefore, an augmented irritability of the vasoconstrictor center."

In producing a rise in blood pressure, epinephrin, reaching the nerve endings in the vessel walls by way of the blood itself, is a stimulus of approximately the same force whether the drug be injected before or after shock has been induced: (It is possible that on account of the great slowing of the circulation the concentration of the epinephrin in the blood in a given organ is less than would normally occur if it were mixed quickly by rapidly flowing blood.) But if there is a state of increased vasomotor irritability in anaphylactic shock, the pressor effect of a standard dose of nicotin would be increased. Such a stimulus might be able, therefore, to overcome the torpor or partial paralysis of the nerve endings in the vessel walls and even to produce an augmented rise in pressure.

[15] Amer. Jour. Physiol., 1916, 40, p. 360.

There is the further possibility that of two stimuli which reach a vessel wall, that one which arrives by way of a nerve, as does the stimulus of nicotin, may be better able to produce its effect under adverse conditions, than a chemical stimulus which reaches the vessel wall through the blood stream.

If there is a state of increased vasomotor irritability in anaphylactic shock it does not develop immediately, but only after the lapse of a few minutes. Whether the failure to obtain any reaction to either epinephrin or nicotin immediately after the onset of shock is due to a sudden complete paralysis of the whole vasomotor apparatus with more rapid recovery of the central elements, or to so complete a paralysis of the nerve endings in the vessel walls that even the exalted stimulating power of nicotin is unable to overcome it, or, finally, to the necessity of a sort of incubation period for the full development of increased irritability of the vasomotor center, cannot at present be definitely determined.

There is a second possibility to account for this action of nicotin, namely, its effect on respiration. In the doses used in these experiments, the usual effect was to increase the rate and depth of respiration, sometimes almost to the point of dyspnea. This lasted on an average for about 30 seconds. The negative pressure in the thorax and therefore the suction on the blood in the great veins must have been much increased during this period. It is not difficult to conceive that the pressure of the diaphragm on the abdominal organs coupled with the increased suction on the blood in the vena cava would bring a greater volume to the right side of the heart. Blood in the liver and overfilled veins of the splanchnic area is in the most favorable location to be drawn into the heart under these conditions. Thus it is possible that nicotin does not, in this instance, raise the blood pressure by the usual mechanism at all.

There is no evidence in the experiments here reported of any constriction of the vessels of the lungs as claimed by Schultz.[7] For the blood that reaches the right side of the heart as a result of the injection of nicotin is evidently quickly and easily forced through the lungs and on into the aorta, raising the arterial pressure.

In further support of the view that the effect of nicotin on blood pressure in anaphylactic shock may be due to its action on respiration, it should be noted that Dog A 10 during the period of falling pressure became dyspneic, as shown in Chart 2. During this time the pressure either ceased to fall or the decline at least became much less rapid.

The cause of this dyspnea is not known. No other animal in this series showed it, altho it was observed once in an animal in peptone shock.

Furthermore, in most of the animals, the injections of nicotin given immediately after the onset of shock did not have any appreciable effect on the respiration. It was only when dyspnea followed the injection of a standard dose of nicotin that the rise in blood pressure occurred. Animal A 10 is unique in that the first injection of nicotin after the onset of shock caused violent respiratory efforts associated with a rise in blood pressure. This problem will be discussed more in detail in another connection.

The fact that when no dyspnea was produced by an injection of nicotin the effect on the blood pressure was less than the normal response for that animal is suggestive evidence that in anaphylactic shock in the dog there is a reduced irritability of the sympathetic nervous system and possibly of the vasomotor center.

CONCLUSIONS

Anaphylactic shock in the dog is associated with a fall in blood pressure. During the period of low pressure the reaction to injections of epinephrin is either absent or greatly diminished, while the response to nicotin may be augmented. It is believed that the mechanism of the latter is chiefly dependent on its effect on respiration, and only to a very limited extent or not at all on direct stimulation of the vasomotor center or the sympathetic ganglia. There is evidence for the belief that there is present a condition of decreased irritability of the sympathetic ganglia and possibly of the vasomotor center. The prompt rise in arterial pressure after injections of nicotin associated with dyspnea is evidence that in anaphylactic shock in the dog there is no constriction of the vessels of the lungs.